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## THE RELATION OF HEREDITY TO CANCER IN MAN AND ANIMALS

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THE existence of hereditary tendencies or predispositions to cancer, in man, has been for years and still is a much debated question. In the face of a steadily increasing volume of evidence both *pro* and *contra*, not only laymen, but the medical profession as well are still of uncertain or divided opinions. Gradually, however, medical institutions have taken up the investigation of the problem until at present a considerable number of laboratories are engaged in experimental studies to determine the importance of heredity in the transmission of cancer. Because of this fact it may be of interest to consider broadly the relation of present genetic methods to the problem of human cancer. We may do this in the hope of determining in advance, if possible, the necessary limitations in applying such methods to the problem in question.

Two main lines of research in genetics may contribute data which have a definite bearing on the question as to whether or not there are hereditary tendencies to cancer in man. The first of these is a study of family histories in human beings themselves; the second is the experimental study of inheritance in the lower mammals.

The value of any data obtained must obviously be based on its scientific accuracy and on its applicability to the problem under consideration. We may now briefly consider the obtainable data in the two branches of research indicated and apply to them the test of value, above mentioned.

All data involving several generations of human beings are of necessity, under our present methods, based at least partly on "hearsay" evidence. The amount of data so obtained when compared with those obtained by direct observation will of course vary in different individual problems. It will, however, always be present as a source of fundamental inaccuracy.

There are many other minor, but none the less important, sources of error. Among these may be mentioned ignorance as to the exact cause of death or diagnoses based on clinical rather than autopsy data. Failure to give sufficient prominence to age, as an important factor, may further complicate the problem. Numerous similar conditions combine with those mentioned to make the data gathered from available sources entirely unreliable in determining the course of inherited tendencies to cancer in the human race.

The accuracy of the data obtained from experimental studies of the

smaller mammals is, on the other hand, sufficient to warrant reliance being placed upon them. Among the smaller mammals, none appear to offer material so favorable to the problem in question as do mice. Their short life cycle, rapidity of multiplication, convenient size and adaptability are supplemented by a varied and representative series of neoplasms serving to give them a unique value. Such studies as those of Tyzzer and Murray, and more recently those of Slye, Loeb and Lathrop, *have proved beyond question that hereditary factors play an extremely important part in determining the incidence of cancer in mice.* Though the *fact of inheritance is undoubtedly established, the method of inheritance is as yet undetermined.* Doctor Slye's work has repeatedly shown that non-cancerous parents may give cancerous offspring, and that cancerous parents may give non-cancerous offspring. This at once indicates a complicated type of inheritance, the exact nature of which is still in doubt.

Even in the case of inoculated tumors in mice, where our sole concern is *growth of the tumor after its implantation*, we have recently found that the interaction of many hereditary factors is involved (Little & Tyzzer, 1915).

Although smaller animals, as shown above, possess great advantages over man as material for studying the influence of heredity on the occurrence of spontaneous cancer, they, nevertheless, because of the fact that they are commonly genetically heterogenous, and because cancer is a disease influenced by sex and by the age of the animal, are not free from certain inherent limitations which make the analysis of the hereditary factors, beyond a certain point, extremely difficult. The only possible exception to this statement will be a race of animals so closely inbred as to be essentially homogeneous in its hereditary constitution. Various geneticists as, for example, Pearl and Jennings, have computed with accuracy the amount of inbreeding necessary before such a condition of homogeneity is closely approached. From their work it appears that many generations of continuous closest inbreeding, such as, for example, own brother and sister matings, must be made before homogeneity of genetic constitution is approximated. It is safe to say that none of the material thus far employed in investigations with spontaneous tumors meets this requirement.

Some doubt has been expressed as to the applicability of the results obtained with small mammals such as mice, for example, to the problem of human cancer. In so far as these results may affect the acceptance of the *fact of heredity*, doubts are not justified by analogy with any of the cases of inheritable characters, so far investigated. It is possible and permissible to argue the existence of hereditary tendencies to cancer in man on the basis of proved existence of such tendencies in other mammals. Similar arguments have been shown to apply to albinism, spotting, shape of hair, color of eyes, certain abnormalities in growth of the bones, and to many other characters.

It further appears that certain histories of human families are striking enough, even with present imperfect methods of obtaining data, to indicate strongly the presence of hereditary tendencies to cancer in man. Not only is this the case, but the problem may be approached from the opposite viewpoint and the data supposed to show the non-inheritable nature of human cancer may be examined. Such work as that of Pearson, and other biometricalians, while adding little in accuracy to the methods of obtaining data on human inheritance, are guilty of a gross mistake in their method of analysis. Their weakness lies in the fact that they are able to detect only the direct or Galtonian type of inheritance and are utterly unable to recognize or utilize the well-defined and accepted principles of transmission by individuals of hereditary potentialities throughout an indefinite number of generations without any morphological manifestation of those potentialities until similar or otherwise suitable mates appear. Biometrical methods are of undoubted value, but they fall short of the whole truth, and can not in this case be taken as alone disproving the occurrence of hereditary factors in the case of human cancer.

An example of an actual case of inheritance in mice may serve to make clear the limitations of biometric methods of detecting even the fact of inheritance. All pigmented mice are classifiable into two groups, those having solid colored or "self" coats, and those having white spots of varying sizes. In other words, the mouse is either "self" or "spotted" *in appearance*. Supposing a mixed population of let us say 15,000 mice, some of which are "self," some "spotted," and let us try to prove that spotting is or is not inherited. Following certain biometric methods we shall consider the parents and grandparents of each spotted mouse as compared with the same ancestral generations of non-spotted ("self") mice.

Any of the following types of ancestry are possible and have actually been *repeatedly* obtained in the laboratory.

Mating	Mouse Observed	Parents	Grand-Parents
(a) Self.....		Self.....	Self
		Self.....	Self
(b) Self.....		Spotted.....	Spotted
		Spotted.....	Spotted
(c) Spotted.....		Self.....	Self
		Self.....	Self

Between these extreme types of ancestry every possible intergrade has been obtained again and again, so that if we happened by chance to pick matings of the types (*a*) or (*d*), or others approaching them, we should undoubtedly prove the inheritance of spotting to our own satisfaction. On the other hand, if matings (*b*) and (*c*) had happened to have been our experience, we should believe that no such inheritance existed. Generally speaking, a mixed population of spotted animals would form for biometric methods of analysis only confused and inconclusive material on which no conclusion of lasting value could be based.

It has, however, long been known that spotting in mice *is* inherited, and I have recently been able to account for and predict the occurrence of the spotted forms on the basis of the interaction of at least three pairs of hereditary factors showing Mendelian or alternative inheritance. In making the analysis of this problem it was fortunate that in certain races in the laboratory, only one or at most two of the three types of spotting existed together. This fact made possible the recognition of certain relationships between the different types of spotted coat which would otherwise have certainly escaped notice, and without which even an incomplete explanation of the facts would have been impossible.

The case of spotting in mice has been entered into at some length because of the fact that it proves the inadequacy of purely biometric methods to detect or explain a case of heredity even involving as few as three pairs of factors. Moreover, these spotting factors produce a series of forms recognizable in early life, and spotting, unlike cancer, is free from the effects of age, sex or any but the most radical environmental disturbances. To *disprove* inheritance solely by biometric methods in this simple case is impossible, and the same is certainly true in the obviously less simple case of cancer.

If now we turn to a consideration of the human beings as material and of certain facts concerning the biological nature of cancer, we can recognize the handicaps under which we must work, if we attempt to investigate the course of hereditary tendencies to cancer in man.

Biologically, cancer may be considered as consisting of a mass of tissue of local origin manifesting uncontrolled and unlimited growth. The problems of its etiology are therefore essentially those of the factors causing, limiting and directing cell division.

If we for a moment consider the cells of the animal body as units, we can picture the embryo of any mammal, at the gastrula stage, as consisting of essentially *two* types of slightly differentiated cells, ectoderm and endoderm. Each of the two types of cells may figure

tively be considered as a "species" consisting of a number of "individuals" undergoing reproduction by the process of mitosis. There are two very distinct environmental forces in the life of such an embryo. One we may call the "external environment," as exemplified by the surroundings of the embryo, the other we may call the "internal environment" which includes the relationships between cells (individuals) *within* the embryo. During the gastrula stage the *internal* environment is relatively simple, but as the embryo grows we find that complexities appear one after another. As the number of cells (individuals) increase, we find that the number of *types* of cells (species) increase as well (differentiation of tissues). This may be considered largely the result of differences in the internal environment in which certain cells or groups of cells find themselves. Nutrition, and undoubtedly to a large extent internal secretions, play the leading parts among the influences of the internal environment.

The young mammal shortly before sexual maturity has thus reached a point where a steady process of cell division (multiplication of individuals) within many definite types of tissue (many species) is in progress. Now into this more or less balanced condition is introduced the secretions of the newly active sex glands, ovaries or testes, as the case may be. At once the internal environment is fundamentally changed. By the circulation the modifications introduced by these secretions are transmitted through the body, reaching all types of cells in all localities. It is as though in a given isolated geographic unit, populated by a fauna of many species, a certain food tree was introduced in great numbers in addition to the somewhat similar types of food trees formerly there. This new tree provides food which gives certain species of animals in certain localities more suitable nutrition than they have yet obtained. The result is rapid growth and reproduction of that particular species, while the others near it may be unaffected, or may even suffer by the rapid multiplication of the favored species.

It is obvious that changes in the internal environment will be frequent. The cyclic changes of the reproductive system, including also the changes of pregnancy and of lactation, undoubtedly represent fundamental upsets of the equilibrium of the internal environment. The same, of course, holds for retrogressive changes such as accompany the cessation of activity of the reproductive system and the progressive changes of approaching senility.

To any biologist, it will have long ago suggested itself to question the influence of the inherent physico-chemical nature of the cell material. Undoubtedly this is a matter of fundamental importance, for it is in the reaction of the cells to the influences and agencies of the internal environment that initiation, continuation and control of cell

division have their origin. It is also certain that hereditary differences in the nature of the cell material among animals of a single species exist. These differences will naturally be an important factor in the reaction of such material to a given stimulus of the internal environment. For example, we may imagine that a certain type of internal environment may cause the material within the connective tissue of individual (*a*) to show no abnormality of growth, while the material forming the connective tissue of individual (*b*) of the very same species may be inherently different to a point where an identical internal environment will start up uncontrolled growth.

On the other hand, two individuals may have connective tissue which is similar in respect to its reactions to a certain stimulus of given internal environment *X*, but may differ in their internal environments because of differences in amount or exact chemical nature of internal secretions or other important agents. In one animal, connective tissue *Y* might show no effects of internal environment *X*, while in the other the interrelation of connective tissue *Y* with environment *X'* might lead to uncontrolled growth.

This rather lengthy treatment of the subject of internal environment has for an object to emphasize the extremely complicated biological nature of cancer. Occurring as it does, usually in middle or old age, it is at a point most completely removed in time and space from the carriers of the elementary hereditary tendencies—the germ cells. In such an animal as man, where the average age for the appearance of cancer, broadly speaking, is about forty-five to fifty years, the opportunities for the effects of the internal environment to become excessively amplified and complicated are, of course, obvious. Injury as well as inflammation of long duration, long recognized as probable agents in the initiation of uncontrolled or abnormal growth, are also much more likely to be of importance in a very slow-growing mammal such as man, than in a rapidly growing mammal like the mouse. This follows from the fact that the *critical periods* in internal environmental changes in man are in themselves far longer in duration than they are in mice, and an injury or irritation, therefore, has more chance of occurring in one of these periods. In the cases of irritation or injury the inherited nature of the individual is of prime importance. A great number of men may use tobacco to an equal extent and yet only part of them may develop cancer of the buccal cavity. In such cases the irritating stimulus may be equal, but the nature of the reaction of the individual's tissue may differ widely.

Again and again we are driven back to the ground that the nature of the mouse, or of the man, by which we mean the nature of his hereditary living material, determines his physiological reactions to any given environment, and further we may add that it determines to a

large extent the behavior of the fundamental factors influencing his *internal* environment. As we attempt, however, to analyze the important hereditary factors, we are in man faced with certain limiting facts. Inadequate methods of observation, diagnosis and recording; magnified effects of environment due to a long life cycle; small numbers of young, and a deliberate system of out-breeding which completely mixes and confuses the material with which we have to deal, force us to the conclusion that studies of hereditary tendencies to cancer in man as they are at present carried on, will yield little, if anything, of value to the subject under consideration. We may further say that present indications are that genetic studies with lower mammals, while having proved definitely the existence of hereditary tendencies to cancer, indicate that a complex type of inheritance is involved which could at best be of negligible importance as a practical preventive or protective measure in man.

This may give the erroneous impression that genetic studies even with lower animals are superfluous in the field of cancer research. This would be most unfortunate, however, for it appears certain that the *etiology* of cancer is a problem of growth and differentiation and as such is essentially biological in nature. It may therefore be approached perhaps with marked success, through genetic investigations with rapidly breeding small mammals in which a study of the biological factors fundamentally important can, under proper circumstances, be best accomplished.